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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 532552000147	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. PCT/US04/11812	International filing date *(day/month/year)* 16 April 2004 (16.04.2004)	Priority date *(day/month/year)* 16 April 2003 (16.04.2003)
International Patent Classification (IPC) or national classification and IPC IPC(7): A61K 9/127, 9/14, 9/50 and US Cl.: 424/450, 489		
Applicant CELATOR TECHNOLOGIES, INC.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 3 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *(sent to the applicant and to the International Bureau)* a total of 6 sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) _____, containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:
   - ☒ Box No. I Basis of the report
   - ☐ Box No. II Priority
   - ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☐ Box No. IV Lack of unity of invention
   - ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI Certain documents cited
   - ☐ Box No. VII Certain defects in the international application
   - ☐ Box No. VIII Certain observations on the international application

Date of submission of the demand 21 October 2004 (21.10.2004)	Date of completion of this report 14 November 2005 (14.11.2005)
Name and mailing address of the IPEA/ US Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201	Authorized officer J. Roberts for Gollamudi S. Kishore, Ph.D Telephone No. (571) 272-1600

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US04/11812

Box No. I Basis of the report

1. With regard to the **language**, this report is based on:

☒ the international application in the language in which it was filed.

☐ a translation of the international application into English, which is the language of a translation furnished for the purposes of:

☐ international search (under Rules 12.3 and 23.1(b))

☐ publication of the international application (under Rule 12.4(a))

☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

☐ the international application as originally filed/furnished

☒ the description:
pages 1-71 as originally filed/furnished
pages* NONE received by this Authority on
pages* NONE received by this Authority on

☒ the claims:
pages NONE as originally filed/furnished
pages* NONE as amended (together with any statement) under Article 19
pages* NONE received by this Authority on
pages* 72-77 received by this Authority on 03 May 2005 (03.05.2005)

☒ the drawings:
pages 1-34 as originally filed/furnished
pages* NONE received by this Authority on
pages* NONE received by this Authority on

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages
☐ the claims, Nos
☐ the drawings, sheets/figs
☐ the sequence listing (*specify*):
☐ any table(s) related to the sequence listing (*specify*):

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages
☐ the claims, Nos
☐ the drawings, sheets/figs
☐ the sequence listing (*specify*):
☐ any table(s) related to the sequence listing (*specify*):

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US04/11812

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 1-24	YES
	Claims NONE	NO
Inventive Step (IS)	Claims NONE	YES
	Claims 1-24	NO
Industrial Applicability (IA)	Claims 1-24	YES
	Claims NONE	NO

2. Citations and Explanations (Rule 70.7)

Claims 1-24 lack an inventive step under PCT Article 33(3) as being obvious over VAAGE et al (Int. J. Cancer, 54, pp. 959-964, 1993) by itself or in view of LAM et al.

VAAGE et al teach the therapeutic efficacy of liposome encapsulated vincristine and doxorubicin (entire publication). What is lacking in VAAGE et al is the teaching of kits for the liposomal compositions. However, the supply of the compositions in a kit form is deemed to be within the skill of the art. One skilled in the art would be motivated to use the liposomal compositions of VAAGE et al in a prefilled syringe form since the reference of LAM et al shows the routine practice in the art of using prefilled syringes containing the active agents. The amounts of the active agents in instant claims are deemed to be manipulatable parameters since these depend upon the disease or specific cancer to be treated and the severity of the disease and other factors. Although VAAGE et al do not teach the combination of various anti-cancer drug combinations, it is deemed obvious to one of ordinary skill in the art to select appropriate anti-cancer agents with a reasonable expectation of success since combination chemotherapy is known in the art.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that although VAAGE et al reports the results of an experiment where vincristine and doxorubicin were contained in liposomes and administered together to an in vivo tumor model, there is no mention of the requirement that the delivery vehicles in the first and second compositions be coordinated with respect pharmacokinetic behavior. This argument is not found to be persuasive since instant claims are kit claims and containing specific amounts of the active agents and the application of these agents to obtain a specific pharmacokinetic behavior which translates into therapeutic efficacy is deemed to be manipulatable perameter practiced by the artisan to obtain the best possible efficacy of the drugs.

Claims 1-24 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.

1. A kit for treatment of a subject which kit comprises

in a first container a composition comprising particulate delivery vehicles stably associated with at least one first therapeutic agent;

in a second container a second composition comprising particulate delivery vehicles stably associated with at least a second therapeutic agent;

wherein the delivery vehicles in said first and second compositions are coordinated with respect to pharmacokinetic behavior; and

wherein said kit further contains instructions for administering said first and second composition at ratios of said first and second therapeutic agent that are non-antagonistic and/or wherein the amounts of said first and second compositions in said containers is proportional to a ratio of said first and second therapeutic agent that is non-antagonistic and/or said containers are calibrated to dispense amounts of said first and second composition wherein the ratio of first and second therapeutic agents is non-antagonistic.

2. The kit of claim 1, wherein the containers are syringes.

3. The kit of claim 1, wherein said agents are antineoplastic agents.

4. The kit of any of claims 1-3, wherein said non-antagonistic effect is exhibited over at least 5% of the concentration range where > 1% of relevant cells are affected ($f_a > 0.01$) in an *in vitro* assay for cytotoxicity.

5. The kit of claim 4, wherein said non-antagonistic effect is exhibited over at least 5% of the concentration range such that 10-90% of the cells are affected ($f_a = 0.1$-0.9) in said *in vitro* assay.

6. The kit of claim 5, wherein said non-antagonistic effect is exhibited over at least 5% of the concentration range such that 20-80% of the cells are affected ($f_a = 0.2$-0.8) in said *in vitro* assay.

7. The kit of claim 6, wherein said non-antagonistic effect is exhibited over at least 20% of the concentration range such that 20-80% of the cells are affected in said *in vitro* assay.

8. The kit of any of claims 1-3, wherein said delivery vehicles have a mean diameter of between 4.5 and 500 nm.

9. The kit of claim 8, wherein said vehicles have a mean diameter of less than 250 nm.

10. The kit of any of claims 1-3, wherein said delivery vehicles comprise
liposomes, and/or
lipid micelles, and/or
block copolymer micelles, and/or
microparticles, and/or
nanoparticles, and/or
polymer lipid hybrid systems, and/or
derivatized single chain polymers.

11. The kit of any of claims 1-3, wherein at least one of the agents is selected from the group consisting of a DNA damaging agent, a DNA repair inhibitor, a topoisomerase I inhibitor, a topoisomerase II inhibitor, a cell checkpoint inhibitor, a CDK inhibitor, a receptor tyrosine kinase inhibitor, a cytotoxic agent, an apoptosis inducing agent, an antimetabolite, a cell cycle control inhibitor, a therapeutic lipid, a telomerase inhibitor, an anti-angiogenic agent, a mitochondrial poison, a signal transduction inhibitor and an immunoagent.

12. The kit of any of claims 1-3, wherein the first agent is a cytotoxic agent and the second agent is a cell-cycle inhibitor, or

wherein the first agent is a DNA damaging agent and the second agent is a DNA repair inhibitor, or

wherein the first agent is a topoisomerase I inhibitor and the second agent is a S/G_2- or a G_2/M-checkpoint inhibitor, or

wherein the first agent is a G_1/S checkpoint inhibitor or a cyclin-dependent kinase inhibitor and the second agent is a G_2/M checkpoint inhibitor, or

wherein the first agent is a receptor kinase inhibitor and the second agent is a cytotoxic agent, or

wherein the first agent is an apoptosis-inducing agent and the second agent is a cytotoxic agent, or

wherein the first agent is an apoptosis-inducing agent and the second agent is a cell-cycle control agent, or

wherein the first agent is a telomerase inhibitor and the second agent is a cell-cycle control inhibitor, or

wherein the first and second agents are antimetabolites, or

wherein the first and second agents are cytotoxic agents, or

wherein the first agent is a therapeutic lipid and the second agent is a cytotoxic agent, or

wherein the first agent is a topoisomerase I inhibitor and the second agent is a DNA repair inhibitor, or

wherein the apoptosis-inducing agent is a serine-containing lipid.

13. The kit of any of claims 1-3, wherein the first agent is irinotecan and the second agent is 5-FU or FUDR, or

wherein the first agent is cisplatin (or carboplatin) and the second agent is 5-FU or FUDR, or

wherein the first agent is idarubicin and the second agent is AraC or FUDR, or

wherein the first agent is oxaliplatin and the second agent is 5-FU or FUDR, or

wherein the first agent is irinotecan and the second agent is cisplatin (or carboplatin), or

wherein the first agent is gemcitabine and the second agent is cisplatin (or carboplatin), or

wherein the first agent is methotrexate and the second agent is 5-FU or FUDR, or

wherein the first agent is paclitaxel and the second agent is cisplatin (or carboplatin), or

wherein the first agent is etoposide and the second agent is cisplatin (or carboplatin), or

wherein the first agent is docetaxel or paclitaxel and the second agent is doxorubicin, or

wherein the first agent is doxorubicin and the second agent is vinorelbine, or

wherein the first agent is carboplatin and the second agent is vinorelbine, or

wherein the first agent is 5-FU or FUDR and the second agent is gemcitabine.

14. A method to treat a disease condition in a subject which method comprises administering to a subject in need of such treatment a therapeutically effective amount of a first composition comprising particulate delivery vehicles stably associated with at least a first therapeutic agent and a second composition comprising particulate delivery vehicles stably associated with at least a second therapeutic agent, at substantially the same time,

wherein the delivery vehicles in said first and second composition are coordinated with respect to pharmacokinetics; and

wherein said administering is at a ratio of first therapeutic agent to second therapeutic agent that is non-antagonistic.

15. The method of claim 14, wherein said non-antagonistic effect is exhibited over at least 5% of the concentration range such that 1%-99% of the cells are affected (f_a = 0.01-0.99) in an *in vitro* assay for cytotoxicity or cytostasis.

16. The method of claim 15, wherein said non-antagonistic effect is exhibited over at least 5% of the concentration range such that 10-90% of the cells are affected (f_a = 0.1-0.9) in an *in vitro* assay for cytotoxicity or cytostasis.

17. The method of claim 16, wherein said non-antagonistic effect is exhibited over at least 5% of the concentration range such that 20-80% of the cells are affected (f_a = 0.2-0.8) in an *in vitro* assay for cytotoxicity or cytostasis.

18. The method of claim 17, wherein said synergistic effect is exhibited over at least 20% of the concentration range such that 20-80% of the cells are affected in an *in vitro* assay for cytotoxicity or cytostasis.

19. The method of any of claims 14-18, wherein said delivery vehicles have a mean diameter of between 4.5 and 500 nm.

20. The method of any of claims 14-18, wherein said vehicles have a mean diameter of less than 250 nm.

21. The method of any of claims 14-18, wherein said delivery vehicles comprise liposomes, and/or
lipid micelles, and/or
block copolymer micelles, and/or
microparticles, and/or
nanoparticles, and/or
polymer lipid hybrid systems, and/or
derivatized single chain polymers.

22. The method of any of claims 14-18, wherein at least one of the agents is selected from the group consisting of a DNA damaging agent, a DNA repair inhibitor, a topoisomerase I inhibitor, a topoisomerase II inhibitor, a cell checkpoint inhibitor, a CDK inhibitor, a receptor tyrosine kinase inhibitor, a cytotoxic agent, an apoptosis inducing agent, an antimetabolite, a cell cycle control inhibitor, a therapeutic lipid, a telomerase inhibitor, an anti-angiogenic agent, a mitochondrial poison, a signal transduction inhibitor and an immunoagent.

23. The method of any of claims 14-18, wherein the first agent is a cytotoxic agent and the second agent is a cell-cycle inhibitor, or

wherein the first agent is a DNA damaging agent and the second agent is a DNA repair inhibitor, or

wherein the first agent is a topoisomerase I inhibitor and the second agent is a S/G_2- or a G_2/M-checkpoint inhibitor, or

wherein the first agent is a G_1/S checkpoint inhibitor or a cyclin-dependent kinase inhibitor and the second agent is a G_2/M checkpoint inhibitor, or

wherein the first agent is a receptor kinase inhibitor and the second agent is a cytotoxic agent, or

wherein the first agent is an apoptosis-inducing agent and the second agent is a cytotoxic agent, or

wherein the first agent is an apoptosis-inducing agent and the second agent is a cell-cycle control agent, or

wherein the first agent is a telomerase inhibitor and the second agent is a cell-cycle control inhibitor, or

wherein the first and second agents are antimetabolites, or

wherein the first and second agents are cytotoxic agents, or

wherein the first agent is a therapeutic lipid and the second agent is a cytotoxic agent, or

wherein the first agent is a topoisomerase I inhibitor and the second agent is a DNA repair inhibitor, or

wherein the apoptosis-inducing agent is a serine-containing lipid.

24. The method of any of claims 14-18, wherein the first agent is irinotecan and the second agent is 5-FU or FUDR, or

wherein the first agent is cisplatin (or carboplatin) and the second agent is 5-FU or FUDR, or

wherein the first agent is idarubicin and the second agent is AraC or FUDR, or

wherein the first agent is oxaliplatin and the second agent is 5-FU or FUDR, or

wherein the first agent is irinotecan and the second agent is cisplatin (or carboplatin), or

wherein the first agent is gemcitabine and the second agent is cisplatin (or carboplatin), or

wherein the first agent is methotrexate and the second agent is 5-FU or FUDR, or

wherein the first agent is paclitaxel and the second agent is cisplatin (or carboplatin), or

wherein the first agent is etoposide and the second agent is cisplatin (or carboplatin), or

wherein the first agent is docetaxel or paclitaxel and the second agent is doxorubicin, or

wherein the first agent is doxorubicin and the second agent is vinorelbine, or

wherein the first agent is carboplatin and the second agent is vinorelbine, or

wherein the first agent is 5-FU or FUDR and the second agent is gemcitabine.